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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,609	07/25/2001	Evan C. Unger	UNGR-1599	8279

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EXAMINER

SHARAREH, SHAHNAM J

ART UNIT	PAPER NUMBER
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1617

DATE MAILED: 03/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/912,609

Applicant(s)

UNGER ET AL.

Examiner

Shahnam Sharareh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12, 14-16 and 20-48 is/are pending in the application.
- 4a) Of the above claim(s) 7, 10-11, 21-39, 43-48 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8, 9, 12, 14-16, 20 and 40-42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 03, 2006 has been entered.
2. Claims 1-12, 14-16, 20-48 are pending. Applicant has made an election of species on the reply filed August 26, 2004 wherein the claims are directed to polyethylene glycol-polycaprolactone copolymers, camptothecin, and CRGDC. Claims 1-6, 8-9, 12, 14-16, 20, 40-42 read on the elected species. The search was also expanded to capture other polymeric targeted matrix wherein the polymer is of polyethylene glycol or poly (lactic-co-glycolic acid). Thus, the claims are examined to the extent they read polyethylene glycol-polycaprolactone copolymers (PEG-PCL), polyethylene glycol (PEG) or poly (lactic-co-glycolic acid) (PLGA) as the polymeric matrix; camptothecin as the bioactive agent; and CRGDC as the targeting ligand.
3. Claims 7, 10-11, 21-39, 43-48 are withdrawn as they are not directed to the elected species. This application contains claims 7, 10-11, 21-39, 43-48 drawn to nonelected species. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-6, 16-17, 20, 40-42 have rejected under 35 U.S.C. 103(a) as being unpatentable over Gref US Patent 5,543,158 (Gref) in view of Quay EP 0727225

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(Quay), Ruoslahti et al US Patent 5,981,478 (Ruoslahti), and Wallace US Patent 5,238,714 (Wallace).

5. Gref discloses compositions comprising particles of a solid biodegradable core comprising PEG and PLGA loaded with a chemotherapeutic or immunosuppressive agent. (see col 3, lines 55-60; col 4, lines 45-65; col 12, lines 39-55; col 14, lines 25-65; claims 1-6). The internal solid core of Gref meets the limitations of the instant matrix. Gref states "a wide range of biological active materials or drugs can be incorporated into the polymer at the time of nanoparticle formation." (see col 12, lines 15-17). Gref then exemplified that hydrophobic drugs may be entrapped into the injectable particles (see col 12, lines 43-45). Gref further states that various types of therapeutic compounds may be incorporated or encapsulated within the internal biodegradable core. (see col 6, lines 1-15). Gref teaches that peptide fragments and/or antibodies can be covalently bounded to the outside of particles. (see col 5, lines 20-30; col 6, lines 26-31; col 18, lines 39-47). Such configuration meets the targeting element of the instant matrix system. Gref also teaches oral or injectable compositions that can be lyophilized which also fall within the scope of the instant matrix. (col 16, lines 30-45). Gref states that his particles may be attached to any particle specific ligand which can include peptides. (col 6, lines 18-25). Gref does not teach the instant targeting ligand CRDG or fu.

6. Quay, Ruoslathi and Wallace are used to show that polymeric microcapsules are readily attached to a targeting ligand to improve specific targeting to tissue cells of interest.

7. Quay teaches various ligands that can be conjugated to contrast agents in colloidal dispersions (abstract, page 3, lines 1-20). Such ligands include CAM ligands such as RGD or cyclic molecules including CRGD, which is specific integrins, and CAM ligands (page 7, line 20-page 8, line 62). The targeting ligands of Quay contain at least 2-10 amino acids.

8. Ruoslahti teaches specific targeting ligands such as CRGDC, and that they are more specific than RGD in inhibiting fibronectin attachment to $\alpha 5 - \beta 1$ (abstract; col 8, lines 21-67; col 9, lines 63-67).

9. Wallace teaches process of conjugating amino acid esters to the surface polymers of microcapsules to provide targeting to specific tissue cells (abstract). The polymeric microcapsules of Wallace can be made of PCL or polylactide (see col 1, lines 6-30; col 9, line 39-col 10, line 60).

10. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to conjugate a specific targeting agent such as CRDGC of Ruoslahti to Gref's microparticles to increase specificity of such particles toward a specific tissue cells by employing conjugation methods described by Quay and Wallace. One of ordinary skill in the art would have made such modifications of polymeric microparticles of Gref, because he would have had a reasonable expectation of success in enhancing cell specificity and thus enhancing intended therapeutic outcome.

11. Claims 1-6, 8-9, 12, 14-16, 20, 40-42 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hunter US Patent 6,759,431 (Hunter), in view of Domb et al US Patent 5,578,325 (Domb) and Ruoslahti.

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12. Hunter teaches various forms of polymeric drug delivery systems that may be used for delivery of camptothecin. (Abstract; col 15, line 20; col 74, lines 15-36). The polymeric moieties of Hunter can be in various forms including drug-loaded microspheres or drug loaded polymeric pastes (col 29, line 50-col 31, line 20; col 56, line 50, col 58, line 67). The polymeric moieties of Hunter comprise PCL, PEG or copolymers thereof in the form of diblocks or paste (col 43, lines 10-col 44, lined 20; col 46, lines 5-65; col 56, lines 50-col 57, line 50; col 69, lines 15-65). Hunter explains that the type and concentration of his polymeric carrier can be fashioned to provide a desired release characteristic (col 21, line 46-co 22, line 65). Hunter also teaches targeted drug delivery to improve Hunter's teachings meets the limitations of claims 1-6, 8-9, 12-16. Hunter does not specifically teach the use of specific target peptides such as CRGDC to enhance the tissue specificity of its formulations.

13. Domb teaches that polymeric moieties of PCL or PEG diblock copolymers can be covalently attached to a targeting ligand to enhance their tissue specificity. (col 13, lines 1-15) (col 15, lines 25-line 65; col 21, lines 40-59).

14. Ruoslahti teaches specific targeting ligands such as CRGDC, and that they are more specific than RGD in inhibiting fibronectin attachment to $\alpha 5 - \beta 1$ (abstract; col 8, lines 21-67; col 9, lines 63-67).

15. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to covalently attach a targeting ligand of choice, such as the CRGDC of Ruoslathi to the polymeric drug delivery systems of Hunter, because as elaborated in the art by Domb, one of ordinary skill in the art would have had a reasonable

expectation of success in improving the tissue specificity of Hunter's drug delivery system in modulating $\alpha 5 - \beta 1$ receptor activity.

Response to Arguments

16. Applicant's arguments filed September 1, 2005 have been fully considered but they are not persuasive for the reasons set forth below.

17. With respect to the rejection of claims over Gref in view of Quay, Ruoslahti, and Wallace, Applicant argues that there the primary reference does not teach a targeting peptide that contains between 2 and 100 amino acid residues. (see Arguments at pg 9-10).

18. In response Examiner states that combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion can only establish obviousness, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, not only there is ample suggestion by the references to use a peptide as a targeting ligand, but also there is ample knowledge generally available to one of ordinary skill in the art to reach the instantly claimed invention.

19. As the initial matter, contrary to Applicant's arguments that Gref's teachings encompass the use of a peptide as a targeting agent. Examiner states that there is no statement in Gref limiting targeting agents to antibody fragment. In fact, at col 6, lines 18-25, Gref states that his particles may be attached to a particle specific ligand for a

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given cell. Moreover, Gref provides for the use of any targeting molecule suitable to provide such property. For example, Gref embraces suitable conditions to preserve activity of attached peptides:

**active molecule. Alternatively, the spacing group can be 55
reacted with the biologically active molecule or antibody or
antibody fragment, and then reacted with the hydroxyl group
on the poly(alkylene glycol). The reaction should be accom-
plished under conditions that will not adversely affect the
biological activity of the molecule being covalently attached 60
to the nanoparticle. For example, conditions should be
avoided that cause the denaturation of proteins or peptides,
such as high temperature, certain organic solvents and high
ionic strength solutions, when binding a protein to the
particle. For example, organic solvents can be eliminated 65**

20. At col 15, lines 45-50, Gref states that such targeting ligands are to be covalently bound to the surface of the particle. Therefore, there is ample teaching about using suitable targeting agents. Gref neither teaches away the use of peptides as targeting agents nor limits the use of targeting agents to a subgenus of antibodies exclusive of any peptides chains.

21. Moreover, to establish non-obviousness, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the rejection is based on the combined teachings of the references not merely the teachings of Gref.

22. Accordingly, the cited secondary references meet the shortcomings of Gref by establishing the state of art as to various modes of linking a targeting ligand to a polymeric particle. Wallace teaches Wallace teaches process of conjugating amino acid

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esters to the surface polymers of microcapsules to provide targeting to specific tissue cells (abstract). The polymeric microcapsules of Wallace can be made of PCL or polylactide (see col 1, lines 6-30; col 9, line 39-col 10, line 60). Quay teaches various ligands such as RGD or cyclic molecules including CRGD and specific linking groups that may be used to attach such ligands to a polymeric moiety. (see page 7, line 20-page 8, line 62; page 11, lines 13-25). Ruoslahti teaches that CRGDC are more specific than RGD in inhibiting fibronectin attachment to $\alpha 5 - \beta 1$ (see abstract; col 8, lines 21-67; col 9, lines 63-67). Thus, their combined teachings meet all elements of the instant claims.

23. Applicant also argues that Quay is directed to ultrasound contrast agents and is not related to the art of drug delivery. (see Arguments at page 10). In response Examiner states it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the teachings of Quay are reasonably pertinent to the art of delivering target specific particles.

24. In addition, contrary to Applicant's arguments the art of ultrasound contrast agent and drug delivery has for long overlapped in context to improve delivery of specific agents to a site of interest and the general knowledge available to one of ordinary skill in the art would have led the artisan to employ any teachings in the area of related to such subject including Quay. In fact, Applicant attests to such fact in previously

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obtained patents such as US Patent 5,542,935 titled "Therapeutic Delivery Systems" wherein, Applicant incorporates contrast agents with drug delivery systems to enhance the clinical outcome. Since, such prior art has been published nearly five years prior to the filing date of the instant Application, such knowledge would have been generally available to one of ordinary skill in the art. For such reasons, the rejection is maintained.

25. With respect to the rejection of claims over Hunter in view of Domb and Ruoslahti, Applicant's arguments have been fully considered but are not persuasive. Accordingly the rejection is maintained.

26. Applicant argues that Hunter does not teach a targeting moiety of a peptide moiety with 2-100 amino acids. (see Arguments at pg 11). In response, Examiner states that Applicant appears to selectively ignore numerous teaching of Hunter that falls within the teachings of the instant claims. The fact that Hunter teaches alternative modes of reaching the instant claims, does not amount to the nonobviousness of the instant claims over Hunter. Hunter teaches various forms of polymeric drug delivery systems that may be used for delivery of camptothecin. (Abstract; col 15, line 20; col 74, lines 15-36). The polymeric moieties of Hunter can be in various forms including drug-loaded microspheres or drug loaded polymeric pastes (col 29, line 50-col 31, line 20; col 56, line 50, col 58, line 67). The polymeric moieties of Hunter comprise PCL, PEG or copolymers thereof in the form of diblocks or paste (col 43, lines 10-col 44, lined 20; col 46, lines 5-65; col 56, lines 50-col 57, line 50; col 69, lines 15-65). Hunter explains that the type and concentration of his polymeric carrier can be fashioned to provide a

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desired release characteristic (col 21, line 46-co 22, line 65). Hunter also teaches targeted drug delivery to improve Hunter's teachings meets the limitations of claims 1-6, 8-9, 12-16. Hunter only fails to enumerate the specific targeting peptide. Such teachings are provided by the secondary references as argued in the previous paragraphs. Thus, the rejection is proper.

27. Applicant's arguments amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Accordingly, for the reasons of record the rejection is maintained.

Conclusion

28. **No claims are allowed.**


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SS



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SUPERVISORY PATENT EXAMINER